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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,186	06/02/2005	Niall Gormley	2713-1-016PCT/US	1271

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411 HACKENSACK AVENUE
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EXAMINER

SHAW, AMANDA MARIE

ART UNIT	PAPER NUMBER
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1634

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/537,186

Applicant(s)

GORMLEY, NIALL

Examiner

Amanda M. Shaw

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 3-9 and 12-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 19-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-26 are currently pending. Applicant's election without traverse of Group I in the reply filed on October 6, 2006 is acknowledged.

Claims 3-9, and 12-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Accordingly, Claims 1-2, 10-11, and 19-26 have been examined herein.

Additionally it is noted that in a telephonic interview with the Applicant it was pointed out that claims 21-22 and 25-26 actually belonged in Group I because they are drawn to a method for detecting a methylated cytosine in a template nucleic acid. These arguments were fully considered and it was agreed upon that claims 21-22 and 25-26 should be examined with Group I. Therefore Group I now consists of claims 1-2, 10-11, and 19-26. Group II now consists of Claims 3-9 and 12-18.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 10-11, and 19-26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 and 10-11 are indefinite over the recitation of the phrase "the complementary nucleic acid strand" in claims 1 and 10. There is insufficient antecedent basis for this limitation in the claim. It is noted that the step (b) (i) refers to a "synthetic nucleic acid strand complementary to the template". It is unclear if the "complementary nucleic acid strand" refers to the "synthetic nucleic acid strand complementary to the template" or something else.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 10, 19, 21, 23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (US Patent 6090552 Issued 2000) in view of Cheeseman et al (US Patent 5302509 Issued 1994) and in further view of Gonzalgo et al (US Patent 7037650 Filed 6/2001).

Regarding Claims 1 and 10 Nazarenko et al teach a hairpin primer which comprises a double stranded stem region, a single stranded loop region, and an additional single stranded region extending from the 3' end of the hairpin which acts as a primer (See Fig 1). In the presence of a target nucleic acid, the target binds to the single stranded region extending from the 3' end of the hairpin. Thus Nazarenko et al teach a single stranded template nucleic acid attached to the 5' end of a hairpin and its

complement attached to the 3' end. In the presence of a polymerase and dNTPs the singled stranded region extending from the 3' end of the hairpin is elongated using the target as a template. Nazarenko et al further teach that hairpin nucleic acid has a recognition sequence and a cleavage site and in the presence of a nicking restriction enzyme the elongated strand can be nicked and strand displacement can occur (See Figure 10 and Columns 29-30). Thus the target nucleic acid which is being interpreted as the template nucleic acid is recovered. Additionally the hairpin is being interpreted as a double stranded nucleic acid anchor because the hairpin probes comprise a double stranded stem region.

Nazarenko et al do not teach a method wherein the sequence of the nucleic acid template is determined as dNTPs are added to the 3' end of the hairpin which acts as a primer.

However Cheeseman teach a method for determining the sequence of nucleotides on a template strand of DNA. Specifically Cheeseman teach a single stranded DNA (which acts as a template) hybridized to an oligonucleotide primer. Fluorescently labeled 3'-blocked nucleotide triphosphates, with each of the bases A, G, C, T having a different fluorescent label, are mixed with the bound DNA molecule in the presence of DNA polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown DNA strand. The 3'-blocking group is then removed, setting the system up for the next NTP addition and so on. These steps are repeated until the entire target is sequenced (Abstract). Further Cheeseman teach that there are several benefits of sequencing

while elongation is taking place. For instance Cheeseman states that (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather than four separate preparations (Columns 1-2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko et al by determining the nucleic acid sequence of the template nucleic acid as dNTPs are added to the 3' end of the hairpin which acts as a primer as suggested by Cheeseman. A method of sequencing a nucleic acid in a PCR reaction while the elongation step is taking place has many advantages such as: (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather than four separate preparations as taught by Cheeseman (Columns 1-2).

Further Nazarenko et al do not teach a method wherein after the elongated strand is nicked and strand displacement occurs (thereby recovering the original template), the template strand is then treated with sodium bisulfite and resequenced as dNTPs are added to the 3' end of the hairpin which acts as a primer. Additionally Nazarenko et al do not teach that by comparing the first synthesized sequence and the second synthesized sequence one can detect the presence of a methylated cytosine in the template.

However Gonzalgo et al teach a method wherein DNA is reacted with sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving any 5-methylcytosine residues unchanged (Column 4). This method is routinely used in the art as demonstrated by Gonzalgo as a starting point for methylation analysis because it allows for methylated cytosines to be distinguished from unmethylated cytosines (Columns 3 and 7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko et al by treating the template with sodium bisulfite as suggested by Gonzalgo. A method of treating a nucleic acid sample with sodium bisulfite is advantageous because the treatment allows for methylated cytosines to be distinguished from unmethylated cytosines as taught by Gonzalgo (Column 7). Thus when the template strand is resequenced as dNTPs are added to the 3' end of the hairpin which acts as a primer, the resulting strand is different from the first synthesized sequence because the template strand has been modified. Further it would be obvious to compare the first synthesized sequence and the second synthesized sequence in order to determine which cytosines are methylated.

Regarding Claims 19, 21, 23, and 25 Nazarenko et al teach a hairpin primer which comprises a double stranded stem region, a single stranded loop region, and an additional single stranded region extending from the 3' end of the hairpin which acts as a primer (See Fig 1). In the presence of a target nucleic acid, the target binds to the single stranded region extending from the 3' end of the hairpin. Thus Nazarenko et al teach a single stranded template nucleic acid attached to the 5' end of a hairpin and its

complement attached to the 3' end. In the presence of a polymerase and dNTPs the singled stranded region extending from the 3' end of the hairpin is elongated using the target as a template. Nazarenko et al further teach that hairpin nucleic acid has a recognition sequence and a cleavage site and in the presence of a nicking restriction enzyme the elongated strand can be nicked and strand displacement can occur (See Figure 10 and Columns 29-30). Thus the target nucleic acid which is being interpreted as the template nucleic acid is recovered. Additionally the hairpin is being interpreted as a double stranded nucleic anchor because the hairpin probes comprise a double stranded stem region.

Nazarenko et al do not teach a method wherein the template nucleic acid is treated with sodium bisulfite.

However Gonzalgo et al teach a method wherein DNA is reacted with sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving any 5-methylcytosine residues unchanged (Column 4). This method is routinely used in the art as demonstrated by Gonzalgo as a starting point for methylation analysis because it allows for methylated cytosines to be distinguished from unmethylated cytosines (Columns 3 and 7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko et al by treating the template with sodium bisulfite as suggested by Gonzalgo. A method of treating a nucleic acid sample with sodium bisulfite is advantageous because the treatment allows for methylated cytosines to be distinguished from unmethylated cytosines as taught by

Gonzalog (Column 7). Thus when the template strand is resequenced as dNTPs are added to the 3' end of the hairpin which acts a primer, the resulting strand is different from the first synthesized sequence because the template strand has been modified. Further it would be obvious to compare the first synthesized sequence and the second synthesized sequence in order to determine which cytosines are methylated.

Further Nazarenko et al do not teach a method wherein the sequence of the nucleic acid template is determined as dNTPs are added to the 3' end of the hairpin which acts as a primer. Additionally Nazarenko et al do not teach that by comparing the known template sequence with the synthesized sequence one can detect the presence of a methylated cytosine in the template.

However Cheeseman teach a method for determining the sequence of nucleotides on a template strand of DNA. Specifically Cheeseman teach a single stranded DNA (which acts as a template) hybridized to an oligonucleotide primer. Fluorescently labeled 3'-blocked nucleotide triphosphates, with each of the bases A, G, C, T having a different fluorescent label, are mixed with the bound DNA molecule in the presence of DNA polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown DNA strand. The 3'-blocking group is then removed, setting the system up for the next NTP addition and so on. These steps are repeated until the entire target is sequenced (Abstract). The methods of sequencing taught by Cheeseman provide many advantages such as: (i) the rate limiting step of DNA identification is the rate of a

polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather than four separate preparations (Columns 1-2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko et al by determining the nucleic acid sequence of the template nucleic acid as dNTPs are added to the 3' end of the hairpin which acts as a primer as suggested by Cheeseman. A method of sequencing a nucleic acid in a PCR reaction while the elongation step is taking place has many advantages such as: (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather than four separate preparations as taught by Cheeseman (Columns 1-2).

4. Claims 2, 11, 20, 22, 2, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (US Patent 6090552 Issued 2000) in view of Cheeseman et al (US Patent 5302509 Issued 1994) in view of Gonzalgo et al (US Patent 7037650 Filed 6/2001) and in further view of Chernov et al (US 2004/0086866 Filed 10/2002).

The teachings of Nazarenko, Cheeseman, and Gonzalgo et al are presented above in paragraph 2.

The combined references do not teach that the hairpin probes are attached to a solid substrate.

However Chernov et al teach the use of hairpin probes attached to a microarray for hybridization assays (Para 0013). Chernov further teach that that it was reported that such hairpin DNA probes hairpin probes attached to a chip display higher rates of hybridization and larger equilibrium amounts of captured targets in comparison with linear probes. Further hairpin-DNA-target complexes were thermodynamically more stable (Para 0013).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nazarenko et al by using probes which are attached to a solid substrate as suggested by Chernov. A method of using a hairpin probe attached to a chip for hybridization assays has several advantages such as (i) they have higher rates of hybridization in comparison with linear probes, (ii) there are larger equilibrium amounts of captured targets in comparison with linear probes, and (iii) they are more thermodynamically more stable than linear probes (Para 0013).

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

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obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 10-11, 19-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-5 and 17-18 of copending Application No. 10537188. Although the conflicting claims are not identical, they are not patentably distinct from each other. Specifically, claims 1-2, 19-20, and 23-24 of the instant application and claims 4-5 of copending Application No. 10537188 both encompass methods comprising: providing a single-stranded template nucleic acid attached to the 5' end of a hairpin nucleic acid, wherein the hairpin nucleic acid is self-complementary and has a first restriction site for a nicking endonuclease, said restriction site comprising a recognition sequence and a cleavage site, wherein said

recognition sequence is situated so that said cleavage site is before, at, or beyond the 3' end of the hairpin nucleic acid, and wherein said hairpin nucleic acid is a self-hybrid, and wherein a nucleic acid strand complementary to the template nucleic acid is attached to the 3' end of the hairpin nucleic acid. Both sets of claims further encompass subjecting the nicked hairpin-template-complement nucleic acid complex to conditions whereby the nucleic acid strand complementary to the template nucleic acid dissociates from the template nucleic acid; thereby recovering the single-stranded template nucleic acid. The claims of the instant application are different from the claims of copending Application No. 10537188 because the claims further comprise additional steps which enable one to detect a methylated cytosine in the template nucleic acid. Additionally claims 10-11, 21-22, and 25-26 of the instant application and claims 17-18 of copending Application No. 10537188 both encompass methods comprising providing a single-stranded template nucleic acid attached to a double-stranded nucleic acid anchor, and wherein a nucleic acid strand complementary to the template nucleic acid is attached to the double-stranded nucleic acid anchor, and wherein the double-stranded nucleic acid anchor: (i) has a first end and a second end; and (ii) has a first restriction site for a nicking endonuclease, said restriction site comprising a recognition sequence and a cleavage site, wherein said cleavage site is situated so that said cleavage site is before, at, or beyond the 3' end of the first end of the double-stranded nucleic acid anchor; wherein the single-stranded template nucleic acid is attached to the 5' end of the first end of the double-stranded nucleic acid anchor, and wherein the nucleic acid strand complementary to the template nucleic acid is attached to the 3' end of the first end of

the double-stranded nucleic acid anchor; Both sets of claims further encompass subjecting the nicked hairpin-template-complement nucleic acid complex to conditions whereby the nucleic acid strand complementary to the template nucleic acid dissociates from the template nucleic acid; thereby recovering the single-stranded template nucleic acid. The claims of the instant application are different from the claims of copending Application No. 10537188 because the claims further comprise additional steps which enable one to detect a methylated cytosine in the template nucleic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

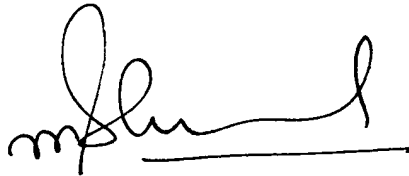
Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

A handwritten signature in black ink, appearing to read 'R. Shukla', with a horizontal line extending to the right from the end of the signature.

**RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER**